A STUDY OF THE BLOOD UREA IN ACUTE SEPSIS AND IN INTESTINAL OBSTRUCTION.

- by -

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The fact that the percentage of urea in the blood may be increased in conditions where there is no disease of the kidneys, has been known for some considerable time. Maclean, in his monograph on renal diseases, points out that various factors such as abstention from fluid for a short time, especially in hot weather, diarrhoea and increased protein intake, may produce a considerable increase in blood urea and he states that in such extra-renal pathological conditions as "cardiac disease, acute or sub-acute intestinal obstruction, pneumonia, empyema, fevers and allied pathological processes" the blood urea may also be increased. Sometimes uraemia has erroneously been diagnosed on this account, and Maclean instances a case of abdominal abscess which was diagnosed as uraemia until further examinations revealed that there was nearly three per cent. of urea in the urine which, he says, "definitely and absolutely excluded the possibility of uraemia."

Tileston and Comfort (1914) published a series of 142 cases of various diseases in which they had studied the blood urea. They claim to have been the

first to observe a rise in the blood urea in intestinal obstruction and this was associated with the ability to excrete over 60 per cent. of phenolsulphonephthalein in the urine in two hours. They state that the increase in bloodurea in this condition is as marked as in most cases of uraemia whether the obstruction be mechanical or paralytic. They attributed this increase of blood urea partly to stagnation of intestinal contents with consequent increased decomposition of nitrogenous substances, and therefore opportunity for greater absorption of non-protein nitrogen from the intestines, partly to the toxic action on the kidney of substances absorbed from the intestines which leads to defective elimination of waste products, and partly to loss of fluid by vomiting with resulting concentration of the blood. Their series includes 14 cases of lobar pneumonia but no other septic conditions. In pneumonia they found the blood urea raised over 35 mgrs. per 100 cc. in 9 out of the 14 cases, but in no case was it over 50 mgrs. per 100 cc. They offered no explanation for this rise in blood urea but stated that it was not dependent on the absorption of the exudate as it occurred before resolution took place.

Schwarz and McGill (1916) published a similar miscellaneous series of 211 cases. In 4 cases of intestinal obstruction they found the blood urea considerably raised. In 20 cases of lobar pneumonia it varied from 12 mgrs. to 104.4 mgrs. per 100 cc. with the maximum rise at the time of the crisis but most

cases showed some retention on the first and second day of disease. 17 of their cases had a definite toxic nephritis as evidenced by an inability to excrete 60 per cent. of phenolsulphonephthalein in the urine in 2 hours. The remaining three were able to excrete the dye adequately and are comparable with the present series. In one of these three cases ending in death the blood urea was 33.6 mgrs. per cent. on the second day of disease, 51.6 mgrs. on the fourth day, and 104.4 mgrs. on the 8th day.

Cooke, Rodenbaugh and Whipple (1916) found the non-coagulable protein of the blood raised in dogs with closed duodenal loops. (As they also performed gastro-enterostomies on these dogs the animals were not obstructed). They obtained a similar rise after giving dogs proteose injections and they thought that this was of importance in explaining the rise of non-coagulable protein in intestinal obstruction and in dogs with closed duodenal loops. They thought that the non-coagulable protein estimation was of more value than the blood urea alone, as the latter varied from 30 to 80 per cent. of the total non-coagulable protein, and forms a much higher percentage of the total nitrogen in nephritis than in intestinal obstructions and loops. They found alterations in the individual nitrogen fractions of the total non-coagulable protein of the blood. The amino-nitrogen and uric acid nitrogen varied within normal limits, the creatin fraction was constantly low, but the creatinine nitrogen was sometimes very high in many

of these cases of proteose intoxication particularly in intestinal obstruction and closed loops; the ammonia-nitrogen was also determined but they stated that their results were inaccurate.

Haden and Orr (1929) thought that the sudden and rapid rises in non-protein nitrogen and blood urea that occurred in dogs with "closed loop obstruction of the jejunum" could only be explained by a great acceleration of protein destruction.

The present investigation was undertaken with the object of determining what effect acute sepsis and intestinal obstruction had on the blood urea, and to see if the estimation of the blood urea could have any practical value in pathological conditions other than those associated with the kidneys.

Technique.

Maclean's modification of Van Slyke's method has been used throughout in estimating the blood urea, and his urea concentration test has been used as the guide to the efficiency of the kidneys or otherwise. The term "efficiency" is used in the sense in which it is commonly employed.

Normal Figures.

There is considerable difference of opinion among various workers as to what is considered the normal blood urea. This divergence doubtless depends upon different methods of estimation. Tileston and Comfort give as normal :

(a) During fasting the blood urea = 12 mgrs. - 14.1 mgrs. per 100 cc.

(b) $2\frac{1}{2}$ Hours after a meal the blood urea = 12 mgrs. - 20 mgrs. per 100 cc.

These figures closely correspond to those of Folin and Denis (11 mgrs. - 13 mgrs. per 100cc.) using

the same technique and to those of Myers (12 mgrs - 15 mgrs. per 100 cc.) who holds that after a fourteen hours' fast a blood urea of over 20 mgrs. per 100 cc. is definitely pathological. Maclean quotes figures somewhat higher, 20 mgrs. - 40 mgrs. per 100 cc. and he says that "the younger the individual the nearer does the value approach to 20 mgrs. per 100 cc., while in older subjects there is a tendency for the upper limit of 40 mgrs. per 100 cc. to be reached or exceeded." In the present series of cases the normal for the individual patient was found by repeating the examination during convalescence whenever the initial figure was thought to be high.

Effect of Diet.

Since urea is mainly a product of exogenous metabolism its percentage in the body will necessarily be affected by the amount of protein ingested. Myers states that the greatest increase in urea nitrogen of the blood comes 5 to 7 hours after a protein meal and according to Tileston and Comfort a full meat diet in healthy adults raises the non-protein nitrogen on an average 4.7 mgrs. per 100cc. and the urea 2.5 mgrs. per 100 cc. This is not a great amount and the effect of diet is perhaps better shown by the reduction in blood urea which occurs on restricting the protein intake of chronic nephritic patients who have a high blood urea. In the present series of cases the diet was necessarily low for hours and in some cases days before admission and so the protein intake can have had little effect on the blood urea.

The excretory function of the kidney has been determined by means of the urea concentration test whenever possible so as to exclude disease of the kidneys as a cause for any increase in the blood urea.

This series consists of 106 cases divided up in the following way :

Appendicitis	38	cases
Other intra-abdominal inflammatory conditions	4	"
Puerperal sepsis	6	"
Miscellaneous abscesses ...	6	"
Non-localised peritonitis ...	5	"
Intestinal obstruction ...	13	"
Pneumonia	21	"
Empyema	11	"
Pleural effusion ...	3	"

One case of appendicitis (case 64) is included both in that group and in the peritonitis group.

Appendicitis.

These cases may be divided into three groups :-

Group 1. The appendix only slightly inflamed - 4 cases.

The blood urea in this group varies from 15 mgrs. to 35 mgrs. per 100 cc. and is therefore not raised to any significant extent.

Group 2. The appendix acutely inflamed but not perforated - 12 cases.

This is a rather larger group with blood ureas varying from 13 mgrs. to 47 mgrs. per 100 cc. Taking 40 mgrs. per 100 cc. as the maximum normal blood urea, 16.6 per cent. of these cases have increased blood ureas, i.e. over 40 mgrs. per 100 cc.

Group 3. The appendix perforated with localised abscess formation - 21 cases.

The blood urea is still higher in this group of

cases. It varies from 15 mgrs. to 58 mgrs. per 100 cc. and 28.5 per cent of the cases have blood ureas of over 40 mgrs. per 100 cc. These patients are also much younger than those in groups 1 and 2 in both of which the average age of the patient is 24 years. In group 3 the average age is 21.8 years and 50 per cent. of them are under 20 years. The question of age is only of importance in assessing whether the blood urea shall be considered normal or not.

Case 33 (table 1) is not included in any of these groups as at operation the appendix was not inflamed; the blood urea in this case was normal - 17 mgrs. per 100 cc.

The temperature was not noted in some of the earlier cases, but the later ones were all febrile (99° - 104°F.) except two (cases 14 and 20 table 1.) which were both in group 3 and both of them had high blood ureas. It seems therefore that the presence or absence of fever and the degree of the fever have no influence on the blood urea in these cases. The urea concentration test was performed in all of the later cases where the blood urea was considered to be high. All of them were able to concentrate urea to about 3 per cent. or over in the urine, so these patients with blood ureas well over 40 mgrs. per 100 cc. behave in this respect as perfectly healthy people.

In seven of the cases a second estimation of the blood urea was made within two weeks of operation. Some of these patients were still febrile and some had had a normal temperature for several days. In four out of the seven the blood urea percentage rose quite remarkably especially about the fourth day after

operation. This may in part have been due to operative trauma and autolysis. The very marked rise from 34 mgrs. to 58 mgrs. per 100 cc. in case 40 (table 1.) has probably a different explanation. Renal inefficiency was excluded by the fact that, a blood urea of 58 mgrs. having been found, the following morning the patient was still able to excrete over 3 per cent. of urea in the second hour specimen of urine after taking 15 gms. of urea. There was, however, considerable difficulty in getting the bowels to act, and it seems that the explanation for some at least of the post-operative increases of blood urea may be that there was a temporary mild obstruction which, as will be shown later, always causes an increase in the blood urea.

A second estimation was not made in four of the earlier cases which had high blood ureas between 45 mgrs. and 58 mgrs. per 100 cc. These patients were all quite young (14, 16, 16 and 29 years respectively) and suffered from no illness apart from their appendicitis, so it seemed fair to assume that the rise in the blood urea was due in some way to their acute condition. Most of these patients with appendicitis vomited a little at the onset of their illness, but in no case was the vomiting excessive or even sufficient to raise the question of dehydration as a cause for the rise in the blood urea. The relationship of a leucocytosis with raised blood urea will be discussed later.

Considering, then, only the blood ureas taken before operation, it is only in cases with local peritonitis (group 3) that there is any significant rise in the blood urea, but the increase is not marked enough and does not occur with sufficient certainty to be of much use in pre-operative diagnosis or in prognosis in simple appendicitis.

TABLE I. Cases of Appendicitis.

GROUP I.

No. of Case	Sex and Age	Blood Urea in Mgrs. %	U.C.T.	Leucocytes per c.m.m.	Temperature	Remarks
3	M.24	35				
48	F.15	21		14,400 P.= 85%	100.6°F.	Duration 17 hours. Vomiting slight.
57	F.32	15			99.8°F.	Duration 4 days. Vomiting slight.
59	F.18	26		14,000	100.6°F.	Duration 15 hours.
			GROUP II.			
2	F.22	32				First day of illness.
5	M.20	47				Appendix almost perforated but no peritonitis.
11	M.21	28				Local peritonitis but no abscess.
12	M.34	37				Pus in appendix but no peritonitis.
19	M.18	39			100.0°F.	
21	M.21	Bef. opn. 33.5 10 days after 41			99° - 100° F.	Duration 30 hours.

No. of Case	Sex and Age	Blood Urea in Mgrs. %	U.C.T.	Leuco-cytes per c.mm.	Tempera-ture.	Remarks
22	M.35	35			99° F.	Duration 2 days. Mucosa of appendix gangrenous.
28	M.30	Bef. opn. 28 4 days after opn. 43 8 days after opn. 35	6 days after opn. over 3%	19,400 P= 82%	100.4°F. 99.4°F. 98.0°F.	Duration 28 hrs.
29	M.11	28.5				3rd day of illness.
45	F.46	13			101.0°F.	3rd day of illness.
56	M.17	28				Append. gangrenous but not perforated. Sero-purulent fluid in perit. but no pus.
61	F.14	14			99.4°F.	Duration 24 hrs. vomited at onset.
			GROUP III.			
4	F.8	35				
8	M.18	36			99.8°F.	
9	M.25	22				
10	M.25	34				

No. of Case	Sex and Age	Blood Urea in Mgrs. %	U.C.T.	Leucocytes. per cmm.	Temperature.	Remarks
13	M.14	50		20,000	102.0°F.	Died 2 days after opn.
14	M.29	58			98.4°F.	
15	M.16	50			100.0°F.	
16	M.16	45				
17	M.8	30				
20	M.14	44			98.0°F.	
24	F.34	Bef. opn. 33 2 wks. later 23		18,200	101.0°F. 102.0°F.	Duration 1 wk.
27	M.22	Bef. opn. 30 3 days. after opn. 37 8 days after opn. 25			101.4°F. Normal 99.0°F.	Duration 2½ days. vomited day\ of onset only.
31	M.36	26			101.8°F.	3rd day of illness.
32	F.21	22			101.6°F.	Duration 2 days. vomited much at onset.
40	M.28	Bef. opn. 34 4 days after opn. 58 8 days after opn. 34 17 days after opn. 25	over 3% on 5th day aft. opn.		104.0°F. 100.0°F. 99.6°F. Normal.	Duration 3 days.

No. of Case	Sex and Age	Blood Urea in Mgrs. %	U.C.T.	Leucocytes. per c.mm.	Temperature.	Remarks.
42	F.52	1 day after opn. 38 9 days after opn. 14 16 days after opn. 27			99° - 100.0°F. 103.0°F. 98.0°F.	Ill for 1 week. General condition poor. General condition much better.
49	F.16	15			101.0°F.	
51	M.17	21			100.2°F.	
60	M.10	20			101.6°F.	Duration 3 days. Vomiting slight at onset only.
64	M.28	53 5 days after opn. 37	over 3%		100.0°F. Normal 4 days.	
68	F.48	25			101.0°F.	Onset 2 days bef.
		Not in any of these Groups.				
33	F.17	17			98.0°F.	? slight congestion of appendix only.

U.C.T. = Urea concentration test.

P. = Polymorphs

Opn. = Operation.

Other intra-abdominal inflammatory lesions.

See Table II.

Two cases of acute cholecystitis in which the diagnosis was confirmed at operation, and two cases of salpingitis are included under this heading. In none of these cases was the blood urea raised before operation. In case 1 M. aet 30 (Table 2), there was an abscess round the duodenum but no generalised peritonitis, and a blood urea of 33 mgrs. per 100 cc. cannot be considered abnormal for a man of his age. This was the highest figure obtained before operation in these cases. Case 30 (Table 2) is interesting on account of the enormous increase of blood urea shortly after operation. The patient vomited copiously and continuously for the first 4 days after operation and as this was thought to be something more than "post-anaesthetic vomiting" the blood urea estimation was repeated to see what effect this vomiting had had. The patient was not noticeably "dehydrated." The table shows the remarkably high figures obtained, and after 11 days the blood urea was again perfectly normal. Urea concentration tests were performed several times. The first time was two days after the maximum blood urea was found, i.e. when the blood urea was probably still about 200 mgrs. per 100 cc. The patient vomited most of the urea and so the figure 2.4 per cent. is probably too low and should be about the normal 3 per cent. These findings of a high blood urea with normal urinary urea are just what would be expected if the renal threshold for urea is raised. The anomalous feature of the case, however, is the low blood urea with low urinary urea found on the 11th day after operation. At first sight it seems that the renal

efficiency (using the term in its ordinary sense) is impaired but if that were so surely the renal impairment, as evidenced by poor urea concentrating power, should have been most obvious on the fourth day after operation when the blood urea was at its highest, and not on the 11th day when the blood urea was lowest. Then, too, if there had been any real damage to the kidneys it is hardly to be expected that they should recover so rapidly as is the case, for by the 18th day the urea concentration test was practically normal. It is probable that the whole condition is due to a paralytic obstruction consequent on a spread of the pelvic peritonitis, and the vomiting so produced may have had a secondary part in causing the rise in blood urea. As the patient improved the blood urea gradually fell but the renal threshold for urea remained raised for some little time after, and so, with the threshold still high, a blood urea of 33 mgrs. per 100 cc. is not a sufficient "head" to enable the kidneys in that state to excrete urea adequately. Subsequently, the action of the proteose, or the substance which it is thought may affect the renal threshold, is removed and so both the blood urea and urea concentration tests become normal.

TABLE II.

No. of Case	Sex and Age	Disease	Blood Urea in Mgrs. %	U.C.T.	Temperature	Remarks.
1	M.30	Cholecystitis	33			L.= 20,000 Abscess round duodenum. No generalised peritonitis.
30	F.31	Bilateral Salpingitis	at opn. 30.5 4 days aft. opn. 238 7 days aft. opn. 155 11 days aft. opn. 33 19 days aft. opn. 35	6 days aft. opn 2.4% 1.85% 18 days aft. opn 2.95%	102.0°F. 100.0°F. 99° - 100.0°F. 100.0°F. Normal to 99°F. for 3 days.	Pelvic peritonitis becoming generalised. Vomiting copiously. General condition better. Discharged cured.
41	F.43	Cholecystitis	29		Normal	L= 16,400 gallstones at opn.
58	F.35	Salpingitis	28		99° - 100°F.	L= 23,000 Duration 17 days. no opn.

U.C.T. = Urea concentration test.

L.= Leucocytes. per c.m.m.

Opn. = Operation.

Puerperal Sepsis.

These patients were all exceedingly ill. Three of the six had normal blood ureas, and in the other three it was raised. Unfortunately, urea concentration tests could not be performed on account of the local sepsis, and most of these patients had to be catheterized at the time when their blood ureas were high. All of the six cases had high temperatures from 100° to 104°F. There is no relationship between the height of the blood urea and length of time since the confinement, but the relationship between the blood urea and intensity of the infection is interesting. The two patients who died within a week of admission (cases 54 and 65, table 3) had low blood ureas and this may simply be further evidence of failure to react against their infection. The last two cases, however, (cases 67 and 70, table 3) both fought against the most intense sepsis and in the end prevailed. These two patients ran very similar clinical courses and they both developed pelvic abscesses which had to be opened. It is interesting to note that the highest blood urea was found on admission before there was any sign of abscess formation, indeed in case 70 where the abscess was very big, the blood urea immediately after operation was 25.5 mgrs. per 100 cc. less than on admission. There is a certain analogy between these cases and two cases of pneumonia to be described later, which both had a falling blood urea as an empyema developed.

TABLE III. Puerperal Sepsis.

No. of Case	Age	Blood Urea in Mgrs. %	Temperature.	Confinement	Remarks
53	41	22	102.0°F.	11 days before	Disch. after 11 days. Condition satisfactory.
54	29	23	103.6°F.	3 days before	B.C. sterile. Died 6 days later.
62	25	40 7 days later 27	101.0°F. Normal for 3days	1 week before	B.C. sterile disch. cured 10 days later.
65	27	24	100° - 103° F.	6 days before	B.C. sterile. D. 6 days later.
67	23	57.5 2 months later 31	104.0°F. Normal for 2 wks	4 days before	B.C. sterile. Disch. cured 9 wks. later. Pelvic abscess & abscess of thighs.
70	27	66.5 3 days later 55 14 days later 41	103.0° F.		B.C. sterile. Abdo. abscess opened. Blood for B.U. taken 2 hrs. after. Still in, improving.

B.C. = Blood culture.

B.U. = Blood Urea.

D. = Died.

Miscellaneous Abscesses.

This small Group (table 4) is composed of cases of abscess formation outside of the abdomen and consists of cases of localised abscesses in bone and subcutaneous tissues.

TABLE IV.

No. of Case	Sex and Age	Disease	Blood Urea in Mgrs. %	Temperature	Remarks
25	M.27	Abscess of neck	29		
39	F.18	Pre-patellar bursitis	32 After Temp. Normal 25	102.8°F.	Duration 2 days, much pus.
43	M.14	Acute Osteo-myelitis	32 After Temp. Normal 25	102.0°F.	Ilium.
44	F.16	Sub-maxillary abscess	22	99.8°F.	Duration 6 days
47	M.14	Frontal sinus abscess	28	100.4°F.	Duration 5 days.
50	M.8	Acute Osteo-myelitis	15	101.0°F.	Left tibia.

In cases 39 and 43 (table 4), where blood ureas of over 30 mgrs. per 100 cc. seemed high for patients under 20 years of age, a subsequent examination showed that the urea percentage did fall after the temperature of the patient became normal. The difference, however, is so slight

as to have no great significance and the conclusion is that in these cases of small abscess formation the blood urea is normal or only very slightly raised.

Peritonitis.

This group includes cases of more generalised peritonitis and not cases where the inflammation has been shut off with localised abscess formation. It is a small group but interesting on account of the case of perforation of the intestines in the third week of typhoid fever, the patient was therefore suffering from acute generalised peritonitis and the blood urea was remarkably high, 225 mgrs. per 100 cc. Unfortunately, he died very soon after admission, and so no further examinations could be made.

Case 64 (table 5), which was also included among the cases of appendicitis, had generalised peritonitis. The blood urea was one of the highest obtained in cases of appendicitis and the increase was probably largely due to the peritonitis. As in the other cases of this series the urea concentration test was over 3 per cent. although the blood urea of 53 mgrs. per 100 cc. is as high as is seen in many cases of nephritis. The patient improved rapidly and 5 days after operation, the temperature having been normal for 4 days, the blood urea had fallen to 37 mgrs. per 100 cc.

In case 34 (table 5), M. aet. 10, the blood urea

of 28 mgrs. is considered slightly high for the patient's age.

There was no increase in the blood urea in the one case of tuberculous peritonitis examined.

In acute generalised peritonitis the blood urea may be very much raised or only a little above the normal. The intensity of the illness can hardly be the determining factor, for the woman with pelvic peritonitis (case 69, table 5) had only been ill for 12 hours and was as acutely ill and toxic as any of the patients examined, and died the day after admission. On the other hand, the child (case 34, table 5), with general peritonitis had been ill for three days but there was no appreciable difference in the blood ureas of these two. The high figure in case 7 (table 5), is only to be compared with that found in cases of intestinal obstruction. There are no notes as to whether this patient had clinical signs of obstruction, but a paralytic ileus is a well-recognised complication of peritonitis and it seems likely that very high blood ureas in general peritonitis are due to an accompanying paralytic ileus rather than to the peritonitis per se.

TABLE V. Non-localised peritonitis.

No. of Case	Sex and Age	Cause	Blood urea in Mgrs. %	Temperature	Remarks
7		Typhoid perforation.	225	104.0°F.	3rd week of illness. Died.
34	M.10	Idiopathic.	28		Duration 3 days.
52	F.16	Tuberculosis.	21	102.0°F.	L= 8,600.per c.m.m. Diarrhoea and vomiting for 6 days, but no dehydration. Diagnosed at operation, 1-2 days later.
64	M.28	Appendicitis.	53 4 days later 37	100.0°F. Normal for 4 days.	U.C.T. = over 3 %.
69	F.35	Salpingitis.	33	104.0°F.	D. the following evening. Only pelvic peritoneum involved.

L. = Leucocytes.

U.C.T. = Urea concentration test.

D. = Died.

INTESTINAL OBSTRUCTION.

It is in this group of cases that the most pronounced rise in blood urea takes place. Eleven out of thirteen cases examined had high blood ureas and in five of these (cases 6, 38, 46, 66 and 71, table 6), it was very high, i.e. over 100 mgrs. per 100 cc. In all cases where the obstruction was relieved, either with operation or without, the blood urea subsequently fell within normal limits, and this reduction in blood urea may occur as early as four days after operation, as in case 6, where it fell from 108 mgrs. per 100 cc. before operation, to 44 mgrs. per 100 cc. four days after operation. Case 38 (table 6) shows that when the obstruction is unrelieved the blood urea continues to rise until death. This patient vomited more and more and as the vomiting became faecal in character he became markedly dehydrated. Towards the end the patient had marked oliguria which, with the vomiting, made it impossible to repeat the urea concentration test. The oliguria is explained by the dehydration and is not due to failure of the kidneys, for the patient was able to concentrate urea perfectly well only a few days before when the blood urea was also very high.

The blood urea may begin to rise as early as 9 hours after the onset of symptoms of obstruction (cf. case 26, table 6). The lower the obstruction the longer does it take before the blood urea shows any

marked rise.

It seems that cases of paralytic ileus, which is mainly a small intestine obstruction, show the most rapid rise in the shortest time. In case 37 (table 6), (? paralytic ileus) the patient was not very ill, there had been some difficulty in getting the bowels to act and some distention, but this was beginning to pass off when the blood urea was taken. In case 26 (table 6), the rise to 87 mgrs. per 100 cc. on the fourth day after operation is indicative of a passing paralytic obstruction and there was considerable difficulty in getting the bowels to act at this time.

The result of the urea concentration test (2.25 per cent.) in case 66 (table 6) cannot be considered perfectly normal, but this patient had been ill and running a continuous temperature for over two months and it is very likely that there was some element of a toxic nephritis about the case, hardly enough, however, to account entirely for the very high blood urea.

The last case in table 6 (case 71) was exceedingly interesting as the question of diagnosis was involved. On the fifth day after operation for a perforated gastric ulcer the patient became noticeably less well and was inclined to be very drowsy. He had no vomiting and his only discomfort was removed after catheterization, when $2\frac{1}{2}$ pints of

urine were withdrawn. The abdomen was still distended after this and very tympanitic. It was on account of the drowsy, semi-comatose state that uraemia was suspected and so the urea concentration test was performed and the blood urea determined. Uraemia was at once excluded when it was found that the patient could cencentrate urea to over 3 per cent. in the second hour specimen of urine. When, after this, the blood urea was found so enormously raised, a diagnosis of paralytic obstruction from general peritonitis was confidently made and a very grave prognosis given. Looked at from another point of view, this case also shows more than any other the futility of a blood urea estimation only in such cases as this when the question of the function of the kidneys is involved.

An examination of the blood urea may therefore have considerable diagnostic importance, and in a case of "acute abdomen" a blood urea over 100 mgrs. per 100 cc. would be greatly in favour of the diagnosis of intestinal obstruction but a low blood urea would not necessarily exclude that.

TABLE VI. Intestinal obstruction.

No. of Case	Sex and Age	Blood urea in Mgrs. %	U.C.T.	Onset	Cause of Obstn.	Remarks.
6		At opn. 108 4 days later 44	over 3%		strang-lated hernia	Gut black
18	M.69	56			strang-ulated hernia	
23	M.21	50	over 3%	12 hrs. bef.	Inflam. mass at splenic flexure	Died
26	M.66	45 4 days after opn. 87 9 days aft. opn. 58 14 days aft. opn. 47	over 3%	9 hrs. bef.	Ing. hernia	Gut returned, no re-section. Bowels not acting well.
35	F.57	39.5		1 wk. bef.	Carcin-oma of colon.	
36	M.66	33 7 days later 30.5	over 3%	3 days bef.	Strang-ulated hernia	No re-section.
37	F.33	4 days after opn. 46.5 6 days later 34	over 3%	since opn. i.e. 4 days bef.	Paralytic ileus.	? obstructed. Bowels just beginning to act again.

No. of Case	Sex and Age	Blood urea in Mgrs. %	U.C.T.	Onset	Cause of Obstn.	Remarks
38	M.58	150 4 days after opn. 106.5 10 days after opn. 185 15 days after opn. 290 21 days after opn. 382	over 3% not repeated on account of vomiting & oliguria	1 wk. bef.	Carcinoma of sigmoid colon	Died 23 days after opn.
46	M.76	122	Could not be done	3 days bef.	Strangulated hernia	Marked dehydration. Died next day
55	M.72	30		14 hrs. bef.	Strangulated hernia	No resection.
63	F.64	59	Not done as patient died.	History vague	Mesenteric thrombosis	Died
66	F.24	101 16 days later 22	2.25%	some days bef.	Paralytic ileus.	Puerperal sepsis. confinement over 2 mths. bef. Now abdominal distension. Disch. much improved.

No. of Case	Sex and Age	Blood urea in Mgrs. %	U.C.T.	Onset	Cause of Obstn.	Remarks
71	M.68	5 days after opn. 235 6 days after opn. 253 8 days after opn. 192 9 days after opn. 203	over 3% 2.17%		Paralytic ileus	opn. 5 days before. Now drowsy. ? uraemia. Still in.

U.C.T. = Urea concentration test.

Opn. = Operation.

Pneumonia.

Twenty-one cases of pneumonia have been examined. They were all of the lobar type except one, case 18 (table 7). Sixteen of these cases had a blood urea of 40 mgrs. per 100 cc. or over when first examined. Nine of these estimations were made on the 7th to 11th days of disease, six were made on days before the 7th day, and in one the duration of illness was not noted. Of the remaining five cases with initial blood ureas less than 40 mgrs. per 100 cc. two had been ill for 14 days, 1 for 19 days, one for 7 days, and one only four days. There seemed to be no difference clincially between these five cases and the others with raised blood ureas. The cases with normal blood ureas were just as ill and one (case 31, table 7), was moribund.

Considering only the first estimations made on each patient, the blood urea when taken before the 7th day of illness varies from 28 mgrs. to 84 mgrs. per 100 cc., when taken between the 7th and 11th day of illness it varies from 37 mgrs. to 139 mgrs. per 100 cc. The earliest definite rise noted was on the 3rd day (case 28, table7) when the blood urea was 50 mgrs. per 100 cc. in a man of 26 years. No observations could be made on patients in the first and second days of their illness as they were

not admitted to hospital as early as this. Hence it seems that the blood urea may begin to rise very early in pneumonia. It is raised quite markedly in nearly 76 per cent. of cases. The greatest increase occurs between the 7th and 11th days, i.e. about the crisis and in every case where there was a definite crisis the blood urea had always begun to fall after it. There is no relation between the height of the blood urea and the amount of lung involved.

Contrary to the cases of pneumonia reported by Schwarz and McGill who found that 17 of their 20 cases had a definite toxic nephritis, not one of these patients had any evidence of nephritis as shown by the fact that they could concentrate urea to 2.9 per cent. or over although the blood urea was high. The urea concentration test was not performed on cases 29 and 31, because they were moribund, and in some of the other cases where the blood urea was not very much raised, it was deemed unnecessary.

Apart from this question of renal inefficiency, these observations seem to correspond closely to those of other workers. The figures given by Tileston and Comfort who found in no case a blood urea of over 50 mgrs. per 100cc., are certainly lower, but the fact that the figure they give as normal is also considerably lower must also be taken into account, as the lowness of

their figures probably depends simply on a difference in technique.

Case 28 (table 7), requires some consideration on account of the sudden and unexpected rise in the blood urea on the 15th day. The patient was progressing quite favourably, the temperature had been normal for several days, there were no abdominal symptoms and it is difficult to account for this sudden rise in blood urea. If it were caused by the resolving pneumonia it is curious that none of the other cases showed a similar rise when once the blood urea had begun to fall, and as will be shown later autolysis seems to play a very small role in causing a rise in blood urea.

TABLE VII. Pneumonia.

No. of Case	Sex and Age	Blood Urea in Mgrs. %	U.C.T.	Leucocytes Per c.mm.	Temperature	Remarks
3	M.	Just bef. crisis 52 3 days later 32	over 3%			L. lower lobe.
4	M.46	4th day 84 9th day 64 13 day 59 18th day 31	over 3%		falling by lysis Normal for 3 days	
5	M.30	7th day 37			100.0°F.	Whole of R. lung.
7	F.19	42 7 days later 32			102.0°F. Normal.	R. lower lobe.
9	F.20	5th day 55 9th day 44	over 3%		Normal	L. lower lobe.
10	M.27	4th day 66	over 3%			
12	M.18	11th day 55 16th day 47 20th day 32				L. lower lobe. Signs of small empyema. Empyema drained.

No. of Case	Sex and Age	Blood Urea in Mgrs. %	U.C.T.	Leucocytes per c.m.m.	Temperature	Remarks
13	M.19	5th day 68 1 day aft. crisis 55 4 days aft. C. 52 7 days aft. C. 40	over 3%			
15	M.41	7th day 73 11th day 44 14th day 31	over 3%		102.0°F.	Bilateral Day aft. C.
16	M.23	5th day 50 8th day 45 11th day 32	over 3%	20,200 P.= 86%	101.0°F.	R. lower lobe. Crisis 7th day.
17	M.27	10th day 48	3.4%		C. that evening	Both bases.
18	M.60	14th day 65 10 days later 30	over 3%	15,400 P.= 92%	101.8°F. Normal.	Scattered broncho-pneumonia and bronchitis
25	M.62	Day of C. 96 5 days later 55	2.9%	21,400 P.= 91%	103.6°F. Normal	R. lower lobe. Jaundiced.

No. of Case	Sex and Age	Blood Urea in Mgrs. %	U.C.T.	Leuco-cytes per c.mm.	Tempera-ture	Remarks
26	M.21	2 days bef. C. 28 5 days aft. C. 39 10 days aft. C. 35				
28	M.26	3rd day 50 9th day 39 15th day 67.5 20th day 27	over 3%	14,400 P.=61%	102.0°F. Normal Normal Normal	Both bases Day aft. Crisis.
29	M.50	7th day 139	No. specimen obtained		99° - 102.0°F.	Moribund.
30	M.27	4th day 36 7th day 29	over 3%	13,400	101° - 104.0°F.	R. base.
31	M.47	14th day 38	No specimen obtained	31,800	101.0°F.	Moribund. Cyanosis marked.
32	M.48	9th day 54 18th day 37	over 3%		102.0°F. Normal for 3 days	R. lower lobe and L. upper lobe.
35	M.42	19th day 30		22,000 P.= 77%	Normal to 102.0°F.	Developed septi-caemia & died.

No. of Case	Sex and Age	Blood Urea in Mgrs. %	U.C.T.	Leucocytes per cmm.	Temperature	Remarks
36	M.25	7th day 40 8th day 60 10th day 50 16th day 33 21at day 28	over 3%		101.0°F. 100.0°F.	Empyema opened

C. = Crisis.

L. = Left.

R. = Right.

P. = Polymorphs.

U.C.T. = Urea concentration test.

Empyema.

These cases were selected as being among the best to illustrate the effect on the blood urea of extra-abdominal abscess formation. Some of the patients, however, had been ill a month or more and are therfore hardly so "acute" as the preceding groups of cases. All of them had a large amount of pus, which was drained by operation. The blood ureas of these eleven cases varied from 14 mgrs. to 57 mgrs. per 100 cc. Only three of these were over 40 mgrs. per 100cc. and the age of these patients varied from 29 to 45 years. In case 20 (table 8), 38mgrs. per 100 cc. in a child of 7 years should also be counted as high.

There is therefore, not nearly so great or so frequent a rise in empyema as in pneumonia and two of the cases of pneumonia which went on to empyema (cases 12 and 36, table 7) had a falling blood urea as the empyema developed. An examination of the blood urea is therfore considered to be no guide at all as to whether there is an empyema or not, (cf. the last two cases of puerperal sepsis with pelvic abscess formation).

TABLE VIII. Empyema.

No. of Case	Sex and Age	Blood urea in Mgrs. %	U.C.T.	Remarks
1	M.29	57	2.8%	
2	M.30	45	over 3%	
6		36		Much pus, cultures pneumo-cocci
14	22	33		
20	M. 7	38		Ill for 1 month.
21	45	Just bef. opn. 45 6 days later 29		Ill for 5 weeks. Chest full of pus.
22	M.20	22		Temperature 101.0°F.
23	M. 8	19		
27	F.37	14 5 days later 18.5		
33	M.17	22		Empyema opened the day before.
34	F.30	24		Chest full of pus.

U.C.T. = Urea concentration test.

Pleural Effusion.

Three cases of tuberculous pleural effusion (table 9) were examined in order to compare them with the above cases of empyema. It seems that the blood urea may be just as high in pleural effusion as in empyema.

TABLE IX. Pleural effusion.

No. of Case	Sex and Age	Blood urea in Mgrs. %	U.C.T.	Temperature.	Remarks
8	F.36	35		102.0°F.	Clear fluid, cells all small lymphocytes.
11	M.22	58		98.6°F.	Clear fluid, cells all small lymphocytes.
19	F.19	27	2.6%		Clear fluid, cells all small lymphocytes.

Myelaemia and Leucocytosis.

In table 10, the blood ureas in four cases of myelaemia are set out with the corresponding leucocyte count.

The table shows that the blood urea is entirely unaffected in this condition where there is an enormous excess of leucocytes circulating in the blood and being destroyed by autolysis.

TABLE X. Myelaemia.

No. of Case	Sex and Age	Leucocytes per c.m.m.	Blood urea in Mgrs. %
1	24	190,000	21
2	F.16	380,000	27
3	F.41	180,000	29
4	M.50	500,000	19

Both this table and the next (table 11), where leucocyte counts and blood ureas done at the same time in some of the former cases are tabulated, show that there is no relation between the blood urea and the number of leucocytes per c.m.m. of blood.

TABLE XI.

Disease	Blood urea in Mgrs. %	Leucocytes per c.m.m.
Cholecystitis	33	20,000 P. = 90%
Appendicitis	50	20,000
Appendix Abscess	33	18,000
Appendix Abscess	28	19,400 P. = 82%
Cholesystitis	29	16,400
Frontal Sinus Abscess	28	12,000 P. = 73%
Tuberculous peritonitis	21	8,600
Puerperal sepsis	23	24,000 P. = 93%
Salpingitis	28	23,000
Appendicitis	26	14,000
Pneumonia	50	20,200 P. = 86%
Broncho-pneumonia	65	15,400 P. = 92%
Pneumonia	96	21,400 P. = 91%
Pneumonia	67.5	14,400 P. = 61%
Pneumonia with developing carbuncle	29	13,400
Pneumonia	38	31,800
Pneumonia	30	22,000 P. = 77%

Discussion.

From this investigation and from the work of others quoted above it appears certain that the blood urea percentage is often very considerably and may be enormously raised in intestinal obstruction. There is also a marked and fairly constant rise in pneumonia before the crisis, and in general peritonitis especially if associated with paralytic ileus. There is a smaller and less constant rise in other acute inflammatory conditions such as appendicitis, empyema and puerperal sepsis, and an almost negligible rise in cases of abscess formation outside the thorax and abdomen. It is quite remarkable how with these high blood ureas, the concentrating power of the kidneys is unimpaired, as is shown by the fact that these patients could all excrete a urine containing 3 per cent. of urea in the second hour after taking 15 grammes of urea by mouth.

There have been several theories advanced to explain the rise in blood urea in these conditions but most of the work has centred around intestinal obstruction where the increase in blood urea is almost as constant and as marked as in uraemia. Furthermore, this condition lends itself easily to accurate study by means of animal experimentation. It is probable that no one of these theories is entirely sufficient to explain the increase of blood urea in

these cases and more than one factor may play a part in each case.

The causes for an increased blood urea are as follows :-

1. Retention due to insufficiency of the kidneys. Using the term "insufficiency of the kidneys" as it is commonly employed, this factor has been ruled out in all of this series by performing urea concentration tests. It may be however, that the kidneys are altered in some way physically so that the threshold for urea, and consequently the blood urea also, is raised.

2. Inspissation of the blood due to loss of water. This may conceivably be a factor in some cases of intestinal obstruction where there is much vomiting and sometimes marked dehydration of the tissues. Dehydration certainly seems to accentuate the toxaemia of these patients, and Hartwell and Hoguet have shown that life in dogs with intestinal obstruction can definitely be prolonged by giving subcutaneously an amount of fluid equal to that lost by vomiting and excretion. If it were simply a question of concentration of the blood, however, one might reasonably expect to find all the constituents of the blood concentrated in a similar degree, but that is not so. In one of these cases when the blood urea was 238 mgrs. per 100 cc. or about 10 times the normal, the uric acid was 8.6 mgrs. per 100 cc. or about 4 times the

normal, and the creatinine was 3 mgrs. per 100 cc. or twice the normal. In case 38 (table 6) the figures were as follows :-

Urea = 185 mgrs. per 100 cc. i.e. approximately 6 times normal.

Uric Acid = 7.14 mgrs. per 100 c.c. i.e. approximately 3 times normal.

Creatinine = 2.8 mgrs. per 100 cc. i.e. approximately 2 times normal.

Conversely one case of pyloric stenosis with dehydration from profuse vomiting had a perfectly normal blood urea - 26 mgrs. per 100 cc.

Haden and Orr (recorded in another paper, 1929) dehydrated dogs by injecting 50 per cent. sucrose and compared the chemical changes in the blood with those of dogs obstructed at the cardiac end of the stomach. They found considerable differences in the two conditions, and the plasma volume was actually less in obstruction than in simple dehydration; the chlorides rise in dehydration but there is a slight fall in obstruction; the final determination of fibrinogen was twice the initial in dehydration whereas it was four times the initial determination in a shorter period of time in obstruction; the protein was increased by 18.6 per cent. in dehydration and by 33 per cent. in obstruction.

Amongst other workers there seems to be a divergence of opinion as to whether the blood urea is increased in simple dehydration or not. Keith,

working with dogs, found no marked changes in the urea nitrogen, whereas Mackay and Mackay using rabbits, showed a marked increase in the blood urea.

Thus it seems there is no clear evidence that inspissation of the blood can of itself account for the rise in the blood urea in intestinal obstruction, and in the other cases, particularly in pneumonia, where the blood urea is also definitely, if to a lesser degree, increased there was no dehydration.

3. Increase of protein catabolism. If the increase in the percentage of any substance in the blood is neither due to retention from faulty excretion, nor to concentration, it is reasonable to suggest that it is due to a greater production of that substance. It is a generally accepted fact that in fever there is an increased destruction of protein and therefore there should be more urea formed and excreted. In studying the cases of pneumonia there seems to be some support for this hypothesis for it has been shown that the blood urea is increased before and begins to fall again immediately after the crisis, i.e. at the subsidence of the fever. On the other hand, many of the patients with puerperal fever, appendicitis, osteomyelitis, bursitis, etc., were just as febrile as the pneumonia cases, but had normal or only very slightly raised blood ureas. The degree and length of duration of the fever seems to

have no relation either, to the amount of urea found in the blood.

The condition par excellence where there is increased metabolism is hyperthyroidism, and in three cases of exophthalmic goitre Schwarz and McGill found the blood urea slightly raised before operation and it fell after. Tileston and Comfort, however, in their series found the amount of urea normal; It would be interesting to compare the blood urea in septic cases with that in a large series of toxic goitres and to make careful estimations also of the total nitrogen and sulphates in the urine to serve as an index of the amount of protein catabolism.

On the whole, it seems likely that increase of protein metabolism plays a very considerable part in causing the blood urea to rise, but it seems hardly sufficient by itself to account for the enormous increase found in some cases of peritonitis and of intestinal obstruction.

4. Autolysis has been suggested as the cause for the rise in blood urea in pneumonia and large abscesses. It is difficult to see how this can affect the urea although it may cause a rise of uric acid and purin bodies which result from the breakdown of nuclei. Todd and Sandford state definitely that the uric acid in the urine is increased during the absorption of a pneumonic

exudate and very markedly also in myelaemia. This is what would be expected owing to the excessive breaking up of leucocytes, but whereas in pneumonia there may be an increase in the percentage of urea in the blood, in myelaemia there is no increase of blood urea as has been shown above. Nor do the facts of the whole of this series of cases support this theory. If autolysis could account for the rise in blood urea surely it would be reasonable to suppose that the urea should be highest in the cases with the most pus, for example, in empyemata where there are often several pints of pus, but that is not so. Then again, in pneumonia the blood urea may rise as early as the first and second day of disease as stated by Schwarz and McGill and in my investigation also, the greatest rise has been found to occur before the crisis, that is before resolution takes place and autolysis comes into play. The theory of autolysis can only be very doubtfully supported by one case in this series (case 28, table 7).

The evidence, therefore, seems to point to increased protein catabolism as a main factor in causing the rise in blood urea in these conditions. Fever is best regarded as a result rather than as the cause of the increased metabolism, and the height of the fever is therefore of secondary importance and may merely depend on the individual

reaction of the patient, just as children react with high temperatures to quite trivial causes, which would not affect the temperature in adults. Is it possible to go further than this and to discover the reason for the increase of metabolism ? Without having done experiments on the total nitrogen excreted to prove the point, it seems fair to assume that some at least of the very great and rapid emaciation which occurs in intestinal obstruction, is due [redacted] to increased destruction of body proteins, for it has been shewn that dehydration is not sufficient of itself to account for all the facts of the case. Whipple, Stone and Bernheim have shewn fairly conclusively the presence of a proteose substance in the duodenal loop fluid in dogs with closed duodenal loops and intestinal obstruction, and they have found the same proteose substance in peritoneal exudates. This proteose when injected into healthy dogs produces all the symptoms of shock and so on that occur in obstruction, and in a further paper by Whipple, Rodenbaugh and Kilgore, it is stated that "Proteose intoxication causes a striking rise in the incoagulable nitrogen of the blood which may double in amount in a period of three hours." Whipple, Stone and Bernheim showed that when the duodenal mucosa is destroyed by means of fluoride this proteose is not formed, and therefore they conclude that it is formed by the mucosal cells. It

seems possible that a similar proteose may be produced in other tissues as well, such as the lung, peritoneum or pleura, either as a result of bacterial action or interference with the circulation or both. It is interesting to note that both in pneumonia and in intestinal obstruction where the highest blood ureas are found, there is almost certainly some interference with the circulation as well as bacterial toxicity, and this circulatory interference may play a considerable part in aiding the production of the proteose. This proteose may act finally by stimulating the processes of catabolism in the body generally. That being so it might be argued that if the kidneys are excreting perfectly normally, as has been shown to be the case, why is the urea not excreted as fast as it is formed, and the blood urea percentage kept within normal limits ?

Although urea is not usually included among the so-called threshold bodies, it is difficult to see why this distinction should be made between urea (a non-threshold substance) and uric acid for example (a threshold body) (Maclean). There seems no reason why urea should not be considered a threshold body, or to put it in other words, urea may have to be present in a particular concentration in the blood before it can be eliminated by the kidneys. It is proposed, therefore, that in certain conditions, due perhaps to the specific action on the

kidneys of a proteose substance, the renal threshold for urea may be raised so that it is necessary for a greater amount to be present in the blood before excretion through the kidneys can take place.

Apart from these theoretical considerations the subject seems to have some practical importance in dealing with cases of "acute abdomen." Cooke, Rodenbaugh and Whipple in 1916, were convinced that the determination of non-protein nitrogen is of value in acute intoxications; they concluded that a high reading signifies a dangerous grade of intoxication, but that a low reading is not necessarily indicative of a low grade of intoxication as some fatal cases may have a low reading (cf. case 31, table 7). In some cases, particularly after operation, where the exact condition of the patient seems obscure, an examination of the blood urea may reveal a temporary obstruction of the bowels where this was only suspected clinically and therefore it may give an indication of a definite line on which to treat the patient. Case 71 (table 6) illustrates well the value of an estimation of the blood urea in conjunction with a urea concentration test. Here the tentative diagnosis of uraemia was excluded immediately on the laboratory findings and the diagnosis of paralytic ileus was confidently substituted.

Summary.

The blood urea has been examined in 106 cases which include cases of appendicitis, saplingitis, cholecystitis, puerperal sepsis, various abscesses, peritonitis, intestinal obstruction, pneumonia, empyema and pleural effusion. It was also examined in four cases of myelaemia.

Urea concentration tests were performed to exclude nephritis.

The blood urea is raised in some cases of all of these conditions except cholecystitis and uncomplicated salpingitis. It is markedly raised in intestinal obstruction, in pneumonia before the crisis, and in general peritonitis when there is a paralytic ileus.

The rise in blood urea, however great it may be, is always associated with perfectly normal urea concentration tests, and therefore it is not due to a failure of the kidneys to concentrate urea.

An examination of the blood urea may have considerable diagnostic importance in abdominal cases, and a reading over 100 mgrs. per 100 cc. is strongly in favour of intestinal obstruction. A urea concentration test should always be performed as well as estimating the blood urea, especially when a question of uraemia is involved.

The blood urea is no guide as to whether an

abscess or empyema has developed or not.

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